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DAVID M. FOX
PARTNER
(202) 637-5678
DMFOX@HHLAW.COM

COLUMBIA SQUARE
555 THIRTEENTH STREET, NW
WASHINGTON, DC 20004-1109
TEL (202) 637-5600
FAX (202) 637-5910
WWW.HHLAW.COM

May 9, 2002

VIA HAND DELIVERY

Margaret M. Dotzel
Associate Commissioner for Policy
Dockets Management Branch (HFA-09305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; Buprenorphine [Docket No. 02N-0101]

Dear Ms. Dotzel:

We are writing on behalf of a client in response to the notice published on April 9, 2002, by the Food and Drug Administration (FDA) regarding, among others, the proposed increase in the level of international control for buprenorphine. 67 FR 17074 (April 9, 2002). We respectfully request that you support the inclusion of buprenorphine in Schedule I/II of the Single Convention on Narcotic Drugs (the "Single Convention"), and that you include our comments in the medical and scientific evaluation of buprenorphine to be presented by the United States to the World Health Organization. *See* 67 FR at 17075. We make this request because buprenorphine (1) is liable to similar abuse as other drugs listed in Schedule I/II and (2) produces similar ill effects as drugs in Schedule I/II. *See* Single Convention, Art. 3(3)(iii).

In at least ten countries in which buprenorphine is used to treat opiate addiction, buprenorphine has emerged as a prevalent drug of abuse. It has a reputation "on the street" as a low-cost alternative to heroin and is believed to be 20 to 40 times more potent than morphine in its analgesic effects. Experienced drug abusers readily recognize buprenorphine as an opiate; inexperienced users see the

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drug as a "safer" route to a heroin-like high. Buprenorphine is also favored by polydrug abusers who combine buprenorphine with benzodiazepines to achieve a heroin-like rush and euphoric effect. This combination has, however, been associated with at least 120 deaths in Europe and Asia, countering the notion that buprenorphine is safer than other opioid agonists.

Buprenorphine, particularly when made available in high-dose tablets, represents a serious drug of abuse for which the United States should seek the most restrictive level of international control.

I. BACKGROUND

Buprenorphine is a derivative of thebaine, a naturally occurring constituent of opium. Like other narcotics, buprenorphine is an analgesic, but is considered to be 20 to 40 times more potent than morphine. See 53 FR 36886 (Sept. 22, 1988).

Buprenorphine is marketed in the United States as a parenteral drug for the relief of moderate to severe pain. At least two new drug applications (NDA) are pending before FDA seeking approval to market buprenorphine as a sublingual tablet for the treatment of opiate addiction. The proposed products contain a much higher dose of buprenorphine (upwards of 8 mg per tablet) than the currently marketed parenteral product. The tablet also has been marketed in France for the same indication since 1996, in a setting similar to what is envisioned for buprenorphine in the United States. Thus, many (including the United States Drug Enforcement Administration) have opined that the French experience is a reasonable predictor of the abuse liability of the tablet if it were made available in the United States.

Buprenorphine currently is listed under Schedule III of the Convention on Psychotropic Substances (the "Psychotropic Convention"). The World Health Organization, however, is considering listing buprenorphine under Schedule I or II of Single Convention, based on the similarity of buprenorphine's pattern of diversion and abuse with other opiates and the increasing rates of abuse and illicit traffic. WHO, 14 WHO Drug Information 223 (2000). Also, in 2000, the United Nations' International Narcotics Control Board conducted a survey of

burprenorphine use and reported increased abuse of the drug and deaths related to its abuse. *See* United Nations *Report of the International Control Board for 2000* at 28 (2000).

Under Schedule I or II, member states must take steps to limit production and distribution of the drug, exercise control over persons who manufacture or distribute the drug, prepare estimates of national requirements for the drug, and impose strong criminal sanctions against those who divert or traffic the drug. *See* Single Convention, Art. 4(c), 19, 20, 29, 30, 33, and 36.

II. COMMENTS

Under the Single Convention, substances are be placed in Schedule I/II if they are "liable to similar abuse and productive of similar ill effects as the drugs in Schedule I or Schedule II." Single Convention, Art. 3(3)(iii). Drugs listed in Schedule I/II include thebaine (I), heroin (I), methadone (I) morphine (I), hydromorphone (I), hydrocodone (I), oxycodone (I), oxymorphone (I), dextropropoxyphene (II), and codeine (II).1/

As shown below, scheduling under the Single Convention would bring buprenorphine in line with other widely used opioid agonists.

Comment 1

Buprenorphine is "Liable to Similar Abuse" as the Drugs in Schedule I/II

Within the last six months, the Food and Drug Administration (FDA) and the Drug Enforcement Administration (DEA) completed detailed analyses of

1/The Single Convention maintains two other levels of control: Schedule III includes "preparations" of narcotic drugs with little or no abuse liability because the narcotic substance cannot readily be recovered from the preparation; Schedule IV includes Schedule I substances for which the abuse liability far outweighs any therapeutic use (*e.g.*, heroin).

the abuse potential and dependence-producing effects of buprenorphine. These analyses (attached hereto under Tabs 1 and 2, respectively) demonstrate that buprenorphine is "liable to similar abuse . . . as the drugs in Schedule I or Schedule II." Single Convention, Art. 3(3)(iii).

Support for Comment 1

The FDA Analysis

FDA's analysis of buprenorphine highlights numerous studies and reports that, taken together, describe buprenorphine as a potent opiate with an abuse liability that is virtually indistinguishable from the prototypical Schedule I/II narcotics. As discussed in the FDA analysis:

- over 100 deaths in France have been linked to high-dose buprenorphine
- "dependence on buprenorphine is a major concern"
- in the U.S., buprenorphine tablets are "likely to present many of the same abuse problems as the high-dose buprenorphine products currently marketed in France and several other countries"
- buprenorphine tablets in the U.S. will "significantly increase" the level of abuse and cause "new and unanticipated public health problems"
- individuals will use the drug "in amounts sufficient to create a hazard to their health and to the safety of other individuals and the community"
- buprenorphine is injected, snorted, and smoked, and is frequently used in combination with other illicit drugs, to enhance its effects

- diversion, forged prescriptions, pharmacy break-ins, and "doctor-shopping" has been seen in other countries
- other countries have had to implement stringent regulatory controls to deal with abuse and diversion problems
- individuals take buprenorphine on their own initiative, often as an opioid substitute, and buprenorphine scores favorably in subjective "liking" studies
- opioid abusers readily identify buprenorphine as an opioid drug and, according to numerous reports, buprenorphine has emerged as a "pharmaceutical-grade" substitute for heroin.

See Tab 1 at 1-4, 5, 7, 10, 15, and 17.

In addition, there is a strong suggestion in the FDA analysis that high-dose buprenorphine is a gateway drug for first-time and emergent opiate abusers. On the street, it is an inexpensive, pharmaceutical-grade alternative to heroin with a reputation for being safe, even at high doses. It produces a long high that can be boosted with benzodiazepines and is believed to be easier to "kick" than heroin. The relative cost, quality, and availability of buprenorphine tablets clearly presents a far more attractive option to the emergent abuser than illicit heroin. Tab 1 at 15; *see* Tab 1 at 17 ("young people who may be in the early stages of drug experimentation . . . would be at risk and *likely to try buprenorphine if it were available*" (emphasis added)); *see also* INSERM, "Evaluation of Subutex® Availability in the Treatment of Drug Users" (June 1998) (attached as Tab 3) at 51, 52 (describing buprenorphine as "*a transition product* leading to heroin consumption among young persons who take cannabis" or other drugs (emphasis added)).

In short, buprenorphine has the characteristics of a drug with Single Convention Schedule I/II abuse potential, along with the added concern that – in a high dose tablet – it is emerging as a safe, cheap, and easy substitute for heroin.

The DEA Analysis

DEA's analysis presents an even stronger case, finding numerous bases upon which to conclude that buprenorphine "has a *high potential* for abuse." Tab 2 at 9 (emphasis added). Among other things, DEA points to the significant number of overdose deaths in France, the fact that buprenorphine is being diverted in considerable amounts from legitimate channels, and the ample data showing that buprenorphine's physical and psychological effects "are essentially the same as morphine or hydromorphine." Tab 2 at 3, 9-10, 15-16. Among other things, DEA has confirmed that buprenorphine has, since 1996, been trafficked widely (Tab 2 at 15) and that it "ranks among the top drugs most frequently abused" in numerous developed countries (Tab 2 at 16).

The DEA analysis also dispels many of the claims that have been made about buprenorphine's unique "partial agonist activity." DEA cites more than a dozen studies to show that buprenorphine shares discriminative stimulus effects that are more closely aligned with Schedule I/II pure mu agonists than with so-called partial agonists. Tab 2 at 3. Of particular relevance to the international scheduling issue, DEA found that buprenorphine's abuse liability profile is closely related to three substances listed under Schedule I of the Single Convention. According to DEA, buprenorphine "produces euphoric effects similar to hydromorphone and, in most populations, buprenorphine is recognized as morphine or heroin-like." Tab 2 at 10. For example, in a study of opiate-free detoxified heroin abusers, "buprenorphine (0.6 mg, intramuscularly) was identified as heroin, was liked better than equianalgesic doses of morphine or pentazocine and caused considerable euphoria (Bedi et al., 1998)." Tab 2 at 3-4.

Finally, as with the FDA analysis, DEA shows that buprenorphine is especially attractive to emergent opiate users, including "drug naïve individuals and experienced non-dependent opiate abusers." Tab 2 at 4. According to DEA, the published literature shows that buprenorphine has "gained popularity as a heroin substitute as well as a primary drug of abuse." Tab 2 at 6. And, because of its "low cost, easy accessibility, high purity and substantial euphoric effects," buprenorphine – according to DEA – is abused by "a wide segment of the drug abusing population," including "*inexperienced non-dependent initiates to drug abuse.*" Tab 2 at 16; *accord* at 6 (noting popularity of buprenorphine among "young drug naive individuals" and

"non-addicted opiate abusers"); *accord* at 17 ("Data from England, France, Scotland, and Ireland demonstrate that buprenorphine, if available, is *abused by young, non-dependent drug abusers*" (emphasis added)).

Comment 2

Buprenorphine is "Productive of Similar Ill Effects" as Drugs In Schedule I/II

The FDA and DEA analyses could not be clearer: "[T]here is evidence that individuals will take buprenorphine in amounts sufficient to create a hazard to their health and to the safety of other individuals and the community." Tab 1 at 5; *accord* Tab 2 at 7 (buprenorphine "is associated with significant public health risks"). High-dose buprenorphine is associated with physical and psychological dependence, aberrant behavior, and serious and fatal adverse events, putting it squarely within the Schedule I/II cluster of opioid agonists.

Support for Comment 2

According to FDA and DEA, researchers have theorized that buprenorphine is safer, relative to the typical opiate, because it is a "partial agonist" with a "ceiling effect" and a lack of dose-response at high doses. *See, e.g.*, Tab 2 at 9-10. Actual experience has proven otherwise.

First, it appears that the "ceiling" concept has only been established in animal studies. DEA cites a ceiling effect with respect to respiratory depression in rats and dogs. Tab 2 at 9-10. Regarding human pharmacology, DEA only describes studies that "suggest" a ceiling effect. Tab 2 at 10; *see also* Tab 3 at 26 (noting that the "effect plateau is observed only for myosis; it is seen clearly neither with respect to positive subjective effects *nor for respiratory depression*" (emphasis added)). This is weak support, at best, given the importance being attached to the "ceiling effect."

Second, the theory that buprenorphine is "safer" at high doses appears to be of little value in actual use settings. There is ample data showing that the use of benzodiazepines in combination with buprenorphine has a synergistic effect that

essentially overrides the ceiling effect, particularly for respiratory depression. *See* Tab 3 at 25. Benzodiazepines are ubiquitous among drug abusers and addicts. *See* Tab 2 at 9. As one research panel described the issue:

> The warnings given to physicians about combining buprenorphine and benzodiazepines must be reiterated both for prescription purposes and to inform patients emphatically about the risks of taking these substances simultaneously. Informational campaigns already launched among users must be made systematic. But the problem is raised for individuals addicted simultaneously to heroin and to benzodiazepines and who undergo a substitution treatment, given the risks linked to abrupt weaning off benzodiazepines. The answer would appear to lie in combing gradual weaning off benzodiazepines with a gradual increase of the substitution product, beginning with doses that are barely efficacious. *While reasonable from a risk standpoint, such a proposal appears, however, unrealistic to addicted users.*

Tab 3 at 26 (emphasis added).

The experience in France confirms the problem. As summarized in the FDA analysis:

> Between January 1996 and May 2000, numerous deaths in France have been attributed to buprenorphine. The first 20 fatalities were described in the open literature. An additional 117 fatalities, based on data from the Institute of Legal Medicine in Strasbourg and 13 other French forensic centers, have been recorded (Kintz 2000). *Kintz considered the total number of*

buprenorphine-related fatalities in France to be an underestimation of the problem.

Tab 1 at 16 (emphasis added). Most of these deaths have been associated with concomitant use of benzodiazepines. Tab 2 at 17.

In short, DEA maintains that buprenorphine is "a safer drug in overdose than other [U.S.] Schedule II substances *despite the many deaths that have been reported in France.*" Tab 2 at 19 (emphasis added). Buprenorphine may be safer in the laboratory or the clinic, but it has proven to be very dangerous in an uncontrolled setting.

In addition to the "many deaths," buprenorphine has dependence-producing effects that are similar in kind to other Schedule I/II drugs. According to DEA, "buprenorphine was shown to produce . . . morphine-like physical dependence" and "buprenorphine can substitute for heroin and is thought to have a similar psychological dependence profile." Tab 2 at 4, 20.

The French INSERM panel 2/ reported that clinicians have described "a very difficult withdrawal process using buprenorphine" because the withdrawal symptoms swing unbearably between normal and a state of withdrawal. Tab 3 at 17. DEA likewise reported results from a withdrawal study in patients following chronic buprenorphine administration that showed "the withdrawal signs were similar to other narcotics." Tab 2 at 17. The FDA summarized the results from the study as demonstrating that "the intensity of withdrawal was described as comparable to that seen with other substances, codeine (C-II) and dextropropoxyphene (C-II)." Tab 1 at 18. DEA's extensive review of the literature found that "under most conditions, buprenorphine's physiological and psychological effects are essentially the same as morphine or hydromorphone." Tab 2 at 3.

2/The panel was a multidisciplinary task force that studied issues involved in the use of buprenorphine for the treatment of opioid addiction. The panel was convened at the request of the French General Health Administration (Direction Generale de la Sante). The study was conducted and the report was written by INSERM (Institute National de la Santé des Etudes et de la Recherche Médicale), the French counterpart to the U.S. National Institutes of Health.

Finally, the withdrawal syndrome associated with buprenorphine is distinguished by its duration of action. What buprenorphine lacks in intensity it makes up for in a "protracted" and often difficult withdrawal process which, on balance, is no less severe than that of any other Schedule I/II opiate. Tab 2 at 17.

III. CONCLUSION

We respectfully request that the medical and scientific discussion presented by the United States to the World Health Organization reflect our comments and observations.3/ Buprenorphine is liable to similar abuse as other drugs listed in Schedule I/II and produces similar ill effects, *with an additional element of risk* because of its appeal to the young and inexperienced user.

As always, we greatly appreciate your careful attention to this matter.

Sincerely,

David M. Fox

David M. Fox /by Mark D Cram

Attachments

cc: James R. Hunter, CDER, HFD-9

3/We are also incorporating into the record of this proceeding (*see* Tabs 4 and 5, attached hereto) views and information previously provided to FDA in a separate filing.